



Original Article

Comparison between an automatic and a visual scoring method of the chin muscle tone during rapid eye movement sleep



Raffaele Ferri^{a,*}, Jean-François Gagnon^{b,c}, Ronald B. Postuma^{b,d}, Francesco Rundo^a, Jacques Y. Montplaisir^{b,e}

^a Sleep Research Centre, Department of Neurology I.C., Oasi Institute (IRCCS), Troina, Italy

^b Centre d'Études Avancées en Médecine du Sommeil, Hôpital du Sacré-Coeur de Montréal, Québec, Canada

^c Department of Psychology, Université du Québec à Montréal, Montreal, Quebec, Canada

^d Department of Neurology, Montreal General Hospital, McGill University, Montreal, Québec, Canada

^e Department of Psychiatry, Université de Montréal, Québec, Canada

ARTICLE INFO

Article history:

Received 9 November 2013

Received in revised form 17 December 2013

Accepted 19 December 2013

Available online 5 March 2014

Keywords:

REM sleep behavior disorder

Atonia index

REM sleep without atonia

Tonic chin EMG

Phasic chin EMG

Automatic analysis

ABSTRACT

Objective: To compare two different methods, one visual and the other automatic, for the quantification of rapid eye movement (REM) sleep without atonia (RSWA) in the diagnosis of REM sleep behavior disorder (RBD).

Methods: Seventy-four RBD patients (mean age, 62.14 ± 9.67 years) and 75 normal controls (mean age, 61.04 ± 12.13 years) underwent one night video-polysomnographic recording. The chin electromyogram (EMG) during REM sleep was analyzed by means of a previously published visual method quantifying the percentage of 30 s epochs scored as tonic (abnormal, $\geq 30\%$) and that of 2 s mini-epochs containing phasic EMG events (abnormal, $\geq 15\%$). For the computer quantitative analysis we used the automatic scoring algorithm known as the atonia index (abnormal, <0.8). The percentage correct classification, sensitivity, specificity, and Cohen kappa were calculated.

Results: The atonia index correctly classified 82.6% of subjects, similar to the percentage of correct classifications with individual components of the visual analysis (83.2% each for tonic and phasic), and the combined visual parameters (85.9%). The sensitivity and specificity of automatic analysis (84% and 81%) was similar to the combined visual analysis (89% and 83%). The correlation coefficient between the automatic atonia index and the percentage of visual tonic EMG was high ($r = -0.886$, $P < 0.00001$), with moderately high correlation with the percentage of phasic EMG ($r = -0.690$, $P < 0.00001$). The agreement between atonia index and the visual parameters (individual or combined) was approximately 85% with Cohen's kappa, ranging from 0.638 to 0.693.

Conclusion: Sensitivity, specificity, and correct classifications were high with both methods. Moreover, there was general agreement between methods, with Cohen's kappa values in the 'good' range. Given the considerable practical advantages of automatic quantification of REM atonia, automatic quantification may be a useful alternative to visual scoring methods in otherwise uncomplicated polysomnograms.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by absent or greatly diminished physiological atonia during REM sleep and by dream-enacting behavior

[1]. REM sleep without atonia (RSWA) is the required polysomnographic (PSG) hallmark for the diagnosis of RBD; however, the current International Sleep Disorders criteria do not specify cut-offs for atonia. In order to overcome the lack of clear cut-off values for RSWA, during the last 20 years several methods have been proposed for its scoring and quantification, with both visual and automatic computer-based approaches [2]. Among them, only very few have been validated in more than one study, and so reliability and replicability remain unclear. Moreover, most methods to quantitate REM atonia rely on manual visual scoring – this requires specialized expertise (not available in all centers) and involves considerable demands of time and cost, limiting broad applicability.

* Corresponding author. Address: Sleep Research Centre, Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Via C. Ruggero 73, 94018 Troina, Italy. Tel.: +39 0935 936111; fax: +39 0935 936694.

E-mail address: rferri@oasi.en.it (R. Ferri).

¹ Drs Ferri and Montplaisir contributed equally as senior authors.

The aim of this study was to analyze the results obtained with two different methods, one visual [3,4] and the other automatic [5,6], in order to assess their reciprocal agreement on the same dataset.

2. Methods

2.1. Subjects

Eighty patients (62 males and 18 females; mean age, 62.7 ± 9.5 years) who were diagnosed with RBD between 1993 and 2006 at the Sleep Disorders Clinic at the Hôpital du Sacré-Coeur de Montréal were recruited, as well as 80 normal controls (62 males and 18 females; mean age, 61.3 ± 12.0 years). The detailed description of their clinical features and of the recruiting process can be found in an earlier paper [4]. The protocol was approved by the University Hospital ethics committee and patients signed a consent form before their participation.

2.2. Polysomnographic recordings

All participants underwent one night of video-PSG monitoring in the sleep laboratory including a full electroencephalogram (EEG) montage to rule out epilepsy. For both RBD patients and normal controls, sleep was recorded according to the Rechtschaffen and Kales' criteria [7] with standard EEG leads (C3–A2, O2–A1), bilateral electro-oculogram (EOG), and chin electromyogram (EMG) recordings. Respiration was monitored using an oro-nasal thermistor or a nasal cannula and with thoracic and abdominal strain gauges, whereas blood oxygen saturation (SaO_2) was continuously recorded by cutaneous finger pulse oxymeter. None of the patients or controls showed an apnea index (number of apneas per hour of sleep) >10 or an index of respiratory events (apneas + hypopneas) >15 .

As RBD patients usually have RSWA, REM sleep cannot be scored on the basis of chin EMG as in the method of Rechtschaffen and Kales [8]. Therefore, the occurrence of the first REM was used to determine the onset of REM sleep. Termination of REM sleep period was identified either by the occurrence of a specific EEG feature of another sleep stage (K complex, sleep spindle) or EEG sign of arousal, or by the absence of rapid eye movements for three consecutive minutes.

Eleven out of 160 recordings (six RBD patients and five controls) were excluded because of technical reasons that did not allow a correct transformation of the signal into European Data Format [9] for the subsequent automatic computer analysis. Thus the following procedures were carried out on 74 recordings of RBD patients (56 males and 18 females; mean age, 62.1 ± 9.67 years) and 75 controls (57 males and 18 females; mean age, 61.0 ± 12.13 years).

2.3. Visual quantitative analysis of the chin EMG during REM sleep

This analysis was carried out following previously published criteria, adapted to 30 s epochs [3,4]. Epochs were scored as tonic or atonic depending on whether chin EMG activity was present for more or less than 50% of the epoch duration. EMG activity was defined by amplitude of the chin EMG signal of at least twice that of the background or $>10 \mu\text{V}$. Phasic chin EMG density was scored from the submental EMG activity and represented the percentage of 2 s mini-epochs containing EMG events lasting 0.1–10 s, with an amplitude exceeding four times the amplitude of the background EMG activity. The phasic EMG activity can be scored on an epoch, which is scored either as atonic or as tonic. Based on previous findings, REM sleep chin EMG levels were considered to be

abnormal when tonic chin EMG density was $\geq 30\%$ and/or phasic chin EMG density was $\geq 15\%$ [4].

2.4. Automatic quantitative analysis of the chin EMG during REM sleep

For the computer quantitative analysis of the submental muscle EMG activity we used an established automatic scoring algorithm [5,6,10]. The submental muscle EMG signal was digitally band-pass filtered at 10–100 Hz, with a notch filter at 60 Hz and rectified. Subsequently, each sleep epoch included in the analysis was divided into thirty 1 s mini-epochs. The average amplitude of the rectified submental muscle EMG signal was then obtained for each mini-epoch. After a noise reduction procedure [6], the values of the submental muscle EMG signal amplitude in each 1 s mini-epoch were used to compute the percentage of values in the following 20 amplitude (amp) classes (expressed in μV): $\text{amp} \leq 1$, $1 < \text{amp} \leq 2$, ..., $18 < \text{amp} \leq 19$, $\text{amp} > 19$. Muscle atonia is expected to be reflected by high values of the first class ($\text{amp} \leq 1$) whereas phasic and tonic activations are expected to increase the value of the other classes [5,6]. As proposed in previous studies, an index summarizing in a single value the degree of preponderance of the first class was used in REM sleep:

$$\text{Atonia index} = \text{amp} \leq 1 / (100 - 1 < \text{amp} \leq 2).$$

Mathematically, this index can vary from 0 (absence of mini-epochs with $\text{amp} \leq 1$), i.e. complete absence of EMG atonia, to 1 (all mini-epochs with $\text{amp} \leq 1$) or stable EMG atonia in the epoch. The REM sleep atonia index correlates significantly with the percentage of epochs of REM sleep without atonia detected by the method by Lapierre and Montplaisir [3,5].

The algorithm was run blinded to the results of the manual scoring procedure. According to previous findings, REM sleep chin EMG levels were considered to be abnormal when atonia index was <0.8 or <0.9 [6]; however, other cut-off values were also used in this study in order to find the optimum level, from 0.7 to 0.9, with 0.05 steps.

2.5. Statistical analysis

Specificity, sensitivity, positive predictive value (PPV), negative predictive values (NPV), and correct classifications of RBD were computed for the atonia index <0.8 and <0.9 , tonic chin EMG density $\geq 30\%$, phasic chin EMG density $\geq 15\%$, and chin EMG density $\geq 30\%$ or phasic chin EMG density $\geq 15\%$. The accuracy of the different parameters to discriminate RBD cases from normal cases was also evaluated using receiver operating characteristic (ROC) curve analysis and the calculation of the area under the curve (AUC). The linear correlation coefficients between the different pairs of visual and automatic parameters were computed, and the relative data scatterplots were drawn, as well as the corresponding least squares lines. Additionally, the extent of agreement between the different pairs of visual and automatic parameters was quantified by means of Cohen's kappa coefficient [11], which is a standard measure of inter-rater agreement for categorical data which can be interpreted as a measure of agreement that exists beyond the amount expected by chance alone [11]. A value of one indicates perfect agreement; a value of zero indicates that agreement is no better than chance. Although there is no universal concordance on the meaning of the magnitude of the Cohen's kappa value, the strength of agreement can be interpreted as follows [12]: <0.20 'poor', 0.21 – 0.40 'fair', 0.41 – 0.60 'moderate', 0.61 – 0.80 'good', and 0.81 – 1.00 'very good.'

Table 1

Analysis of the performance of the automatic and visual quantitative chin EMG scoring methods used in this study for the diagnosis of RBD.

	Atonia index <0.8	Atonia index <0.9	Tonic EMG $\geq 30\%$	Phasic EMG $\geq 15\%$	Tonic EMG $\geq 30\%$ or phasic EMG $\geq 15\%$
Sensitivity	0.84 (0.74–0.91)	0.96 (0.88–0.99)	0.73 (0.62–0.82)	0.80 (0.69–0.87)	0.89 (0.80–0.94)
Specificity	0.81 (0.72–0.89)	0.51 (0.39–0.62)	0.93 (0.85–0.97)	0.87 (0.77–0.93)	0.83 (0.73–0.90)
PPV	0.82 (0.71–0.89)	0.66 (0.56–0.74)	0.92 (0.82–0.97)	0.86 (0.75–0.92)	0.84 (0.74–0.90)
NPV	0.84 (0.73–0.90)	0.93 (0.79–0.98)	0.78 (0.68–0.85)	0.81 (0.71–0.88)	0.89 (0.79–0.94)
Correct	82.6% (75.6–87.8)	73.2% (66.5–76.1)	83.2% (76.4–88.3)	83.2% (76.4–88.3)	85.9% (79.4–90.6)
AUC	0.83	0.73	0.83	0.83	0.86

EMG, electromyography; RBD, rapid eye movement sleep behavior disorder; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve. Values in parentheses are 95% confidence intervals.

3. Results

Table 1 reports the analysis of the performance of the automatic and visual quantitative chin EMG scoring methods used in this study for the diagnosis of RBD. The automatically computed atonia index with a cut-off value <0.8 classified correctly 82.6% of subjects with relatively high values of sensitivity and specificity; the AUC at ROC analysis was 0.83; the alternative cut-off value of atonia index (<0.9) classified correctly 73.2% of subjects, with relatively higher values of sensitivity (0.96) and lower values of specificity (0.51); the AUC at ROC analysis was also lower (0.73). Sensitivity and specificity of different cut-off values of atonia index are shown in Fig. 1. In both panels, the curves of sensitivity and specificity cross very close to the 0.8 cut-off value. Therefore we chose this cut-off as the most reliable value, and used this in subsequent analyses.

The percentage of correct classifications with each individual visual parameter was very similar (83.2%), as well as the AUC (0.83); however, both parameters showed slightly lower sensitivity and slightly higher specificity than the atonia index. The use of the combined visual parameters correctly classified 85.9% of recordings with a slightly higher sensitivity and AUC than that of the individual visual parameters but with a slightly lower specificity.

Fig. 2 shows the correlation between the different pairs of visual and automatic parameters. The correlation coefficient between the automatic atonia index and the percentage of visual tonic chin EMG density was highest ($r = -0.886$, $P < 0.00001$); also the correlation between atonia index and the percentage of phasic chin EMG

density was significant ($r = -0.690$, $P < 0.00001$), as well as that between the percentage of visual tonic chin EMG density and that of phasic chin EMG density which presented the smallest correlation value ($r = 0.665$, $P < 0.00001$).

Table 2 reports the extent of agreement between the different pairs of visual and automatic parameters. The agreement between atonia index <0.8 and the visual parameters (individual or combined) was ~85% with a 'good' Cohen's kappa, ranging from 0.638 to 0.693. The agreement between the two individual visual parameters was slightly lower (~80%, 'moderate').

4. Discussion

The results of the comparison of the two scoring methods for REM sleep chin EMG atonia obtained in this study show that values of sensitivity, specificity, and correct classifications are high with both methods and are consistently >80%, with some of them touching 90%. Also there was general agreement between the methods, with Cohen's kappa values that are considered in the 'good' [12] range. Moreover, in this study we have found high quantitative correlation between the visual and the automatic parameters, confirming previous preliminary data suggesting a good correlation [5,10].

First of all, it should be mentioned that both methods found that 11–27% of RBD patients show atonia values falling within the expected normal range, as described in the previous validation studies performed for both methods individually [4,6]; conversely, 7–19% of controls show atonia values considered as abnormal.

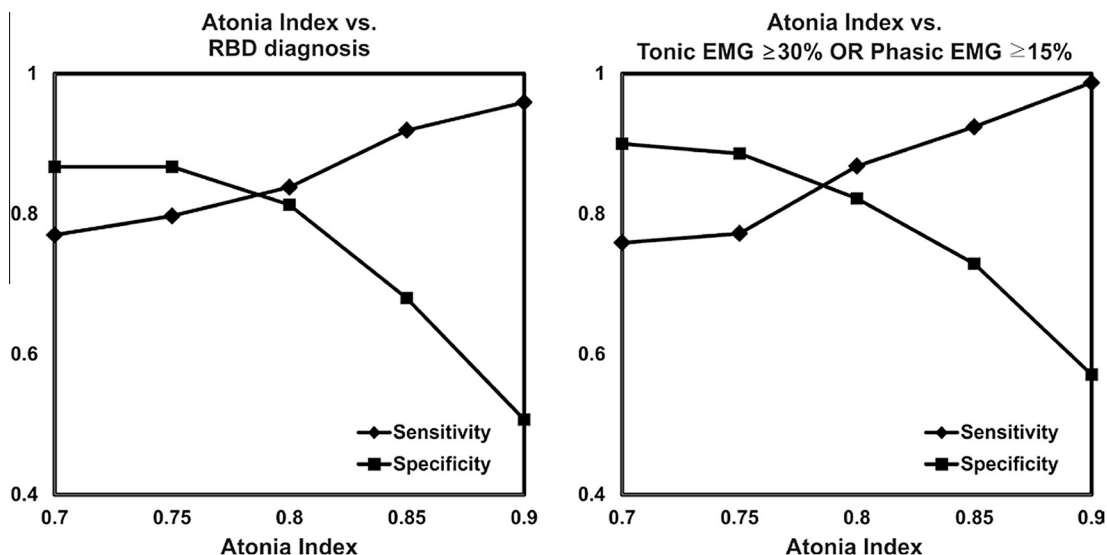


Fig. 1. Sensitivity and specificity of different atonia index cut-off values with respect to the RBD diagnosis or to their classification as abnormal/normal by the visual method (combined tonic and phasic parameters). EMG, electromyography; RBD, rapid eye movement sleep behavior disorder.

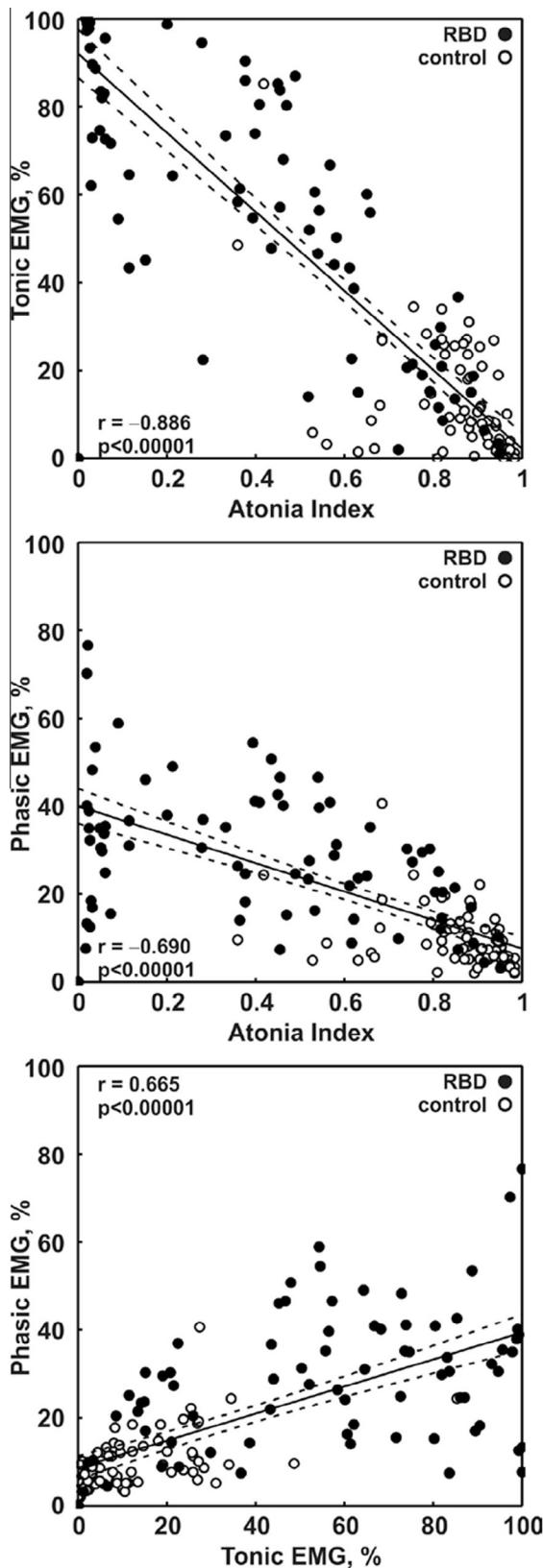


Fig. 2. Correlation between the different pairs of visual and automatic parameters. EMG, electromyography; RBD, rapid eye movement sleep behavior disorder.

There are various reasons for this, both biological and methodological. It is already well known that, in RBD patients, there is night-to-night variability that can partly explain the lack of RSWA in

one single night recording [13,14], used in the present study. In particular, studies using visual quantification of the chin EMG amplitude during REM sleep and video-analysis of behaviors found that only increased tonic chin muscle activity is a relatively stable measure for RBD diagnosis; conversely, enhanced phasic chin activations and motor/vocal behaviors are more variable between nights [13]. Accordingly the atonia index has been found to be more stable than the number of chin muscle activations in both normal controls and idiopathic RBD patients [14]. This variability may also explain the only moderate correlation between phasic and tonic visual parameters and also between the phasic visual parameter and atonia index. Finally, some RBD patients have RSWA limited to the limbs; thus, the analysis of chin might be insufficient in some patients; addition of limb muscle analysis might improve reliability, and should be explored in future studies [15]. Similarly, combining automatic and video-PSG analyses might increase diagnostic accuracy further.

A second biological factor influencing the sensitivity and specificity of the parameters evaluated in this study is the fact that some controls have RSWA. It has been reported that REM chin EMG amplitude normally changes across the lifespan; the atonia index has a progressive and rapid increase until the pre-adolescent age, reaching its maximum in the young adult group. After this age a small decline occurs in middle-aged and elderly subjects [16].

Finally, from the methodological point of view, the establishment of cut-off values for a clinical measure in an index group of subjects will almost inevitably be followed by lower values of specificity and sensitivity when applied to a separate group of subjects. This is an important methodological aspect that should always be considered before accepting a new measure with cut-off values established on a single study and not tested on an independent group of subjects.

Our analysis showed that the <0.8 cut-off value appears to be optimal for identification of definite RSWA in RBD patients. However, previous analyses [6,16–19] suggested that values of atonia index between 0.8 and 0.9 might characterize a mild/moderate abnormality of the chin muscle tone during REM sleep, which could be seen in both RBD patients and normal controls (especially elderly). Therefore, an atonia index <0.8 could be considered clearly abnormal, values >0.9 as clearly normal, and values ranging between 0.8 and 0.9 as indeterminate. Management of patients with intermediate values would vary depending on clinical context and prior probability. Using this method (i.e. considering atonia index <0.8 as abnormal in controls and atonia index <0.9 as abnormal in RBD patients) in this study would have improved sensitivity to 0.96, specificity to 0.82, and correct classifications to 88.6%. Further large-scale multicenter studies might be useful to confirm or further refine the cut-off values used by both visual and automatic methods.

Regardless of the cut-off chosen, a certain portion of controls falls within the RSWA range. It is not clear how these individuals should be considered: they might represent a subgroup of normal controls with impaired REM sleep atonia who will never develop into a disease, or they might constitute a subgroup at risk for developing RBD. If the latter is true, finding isolated RSWA might indicate a preclinical state that may warrant further follow-up. Up to 80% of patients with idiopathic RBD eventually develop a defined neurodegenerative phenotype [20–23], typically a synucleinopathy such as Parkinson disease, Lewy body dementia or multiple system atrophy. The usually long interval between RBD onset and the onset of clinical symptoms of neurodegeneration suggests a potentially wide window for intervention during the preclinical disease stages. If definite RSWA alone is an early stage in the development of RBD, this could further enlarge the window for early neuroprotective intervention. Future research is warranted to define the prognosis of asymptomatic RSWA.

Table 2

Extent of agreement between the different pairs of visual and automatic parameters.

	Agreement (%)	Cohen's kappa
Atonia index <0.8/tonic EMG \geq 30%	84.6	0.693 ('good')
Atonia index <0.8/phasic EMG \geq 15%	85.2	0.638 ('good')
Atonia index <0.8/tonic EMG \geq 30% or phasic EMG \geq 15%	84.6	0.691 ('good')
Tonic EMG \geq 30%/phasic EMG \geq 15%	79.9	0.591 ('moderate')

EMG, electromyography.

Automatic methods present some general advantages over the visual methods because they are fast and replicable, allowing analysis of large datasets. Moreover, the atonia index and its correlated measures appear to be sensitive and specific in differentiating various clinical conditions in whom RBD has been reported, such as multiple system atrophy [5], narcolepsy and idiopathic hypersomnia [10,24], and Parkinson's disease [17]. Finally, the atonia index can be calculated over the entire sleep period, not only during REM sleep; this might represent a potential tool to disclose tone alterations outside of REM sleep [19]. Some disadvantages are incomplete sensitivity of the atonia index method to detecting large artifacts (small artifact activity can be easily corrected [6]) and the fact that most commercial sleep analysis software packages do not include it. Therefore, in the clinical setting, visual methods might be required when the automatic method cannot be applied for technical reasons, or for a second assessment in the case of unexpected or equivocal results obtained with automatic methods.

Funding sources

This study was partially supported by the Italian Ministry of Health ('Ricerca Corrente') and by the Canadian Institutes of Health Research.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2013.12.022>.

Acknowledgment

The authors gratefully acknowledge the technical assistance provided by Ms. Sylvie Rompré.

References

- [1] American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual. Westchester (IL): American Academy of Sleep Medicine; 2005.
- [2] Fulda S, Plazzi G, Ferri R. Scoring atonia during normal and pathologic REM sleep: visual and automatic quantification methods. *Sleep Biol Rhythms* 2013;11(Suppl. 1):40–51.
- [3] Lapiere O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. *Neurology* 1992;42:1371–4.
- [4] Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. *Mov Disord* 2010;25:2044–51.
- [5] Ferri R, Manconi M, Plazzi G, Bruni O, Vandi S, Montagna P, et al. A quantitative statistical analysis of the submental muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. *J Sleep Res* 2008;17:89–100.
- [6] Ferri R, Rundo F, Manconi M, Plazzi G, Bruni O, Oldani A, et al. Improved computation of the atonia index in normal controls and patients with REM sleep behavior disorder. *Sleep Med* 2010;11:947–9.
- [7] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Washington (DC): Washington Public Health service; US Government Printing Office; 1968.
- [8] Kales A, Beall GN, Berger RJ, Heuser G, Jacobson A, Kales JD, et al. Sleep and dreams. Recent research on clinical aspects. *Ann Intern Med* 1968;68:1078–104.
- [9] Kemp B, Varri A, Rosa AC, Nielsen KD, Gade J. A simple format for exchange of digitized polygraphic recordings. *Electroencephalogr Clin Neurophysiol* 1992;82:391–3.
- [10] Ferri R, Franceschini C, Zucconi M, Vandi S, Poli F, Bruni O, et al. Searching for a marker of REM sleep behavior disorder: submental muscle EMG amplitude analysis during sleep in patients with narcolepsy/cataplexy. *Sleep* 2008;31:1409–17.
- [11] Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960;20:7–46.
- [12] Altman DG. Practical statistics for medical research. London: Chapman & Hall; 1991.
- [13] Cygan F, Oudiette D, Leclair-Visonneau L, Leu-Semenescu S, Arnulf I. Night-to-night variability of muscle tone, movements, and vocalizations in patients with REM sleep behavior disorder. *J Clin Sleep Med* 2010;6:551–5.
- [14] Ferri R, Marelli S, Cosentino FI, Rundo F, Ferini-Strambi L, Zucconi M. Night-to-night variability of automatic quantitative parameters of the chin EMG amplitude (Atonia Index) in REM sleep behavior disorder. *J Clin Sleep Med* 2013;9:253–8.
- [15] Iranzo A, Frauscher B, Santos H, Gschliesser V, Ratti L, Falkenstein T, et al. Usefulness of the SINBAR electromyographic montage to detect the motor and vocal manifestations occurring in REM sleep behavior disorder. *Sleep Med* 2011;12:284–8.
- [16] Ferri R, Bruni O, Fulda S, Zucconi M, Plazzi G. A quantitative analysis of the submental muscle electromyographic amplitude during rapid eye movement sleep across the lifespan. *J Sleep Res* 2012;21:257–63.
- [17] Ferri R, Fulda S, Cosentino FI, Pizzi F, Plazzi G. A preliminary quantitative analysis of REM sleep chin EMG in Parkinson's disease with or without REM sleep behavior disorder. *Sleep Med* 2012;13:707–13.
- [18] Ferri R, Marelli S, Ferini-Strambi L, Oldani A, Colli F, Schenck CH, et al. An observational clinical and video-polysomnographic study of the effects of clonazepam in REM sleep behavior disorder. *Sleep Med* 2013;14:24–9.
- [19] Ferri R, Zucconi M, Marelli S, Plazzi G, Schenck CH, Ferini-Strambi L. Effects of long-term use of clonazepam on nonrapid eye movement sleep patterns in rapid eye movement sleep behavior disorder. *Sleep Med* 2013;14:399–406.
- [20] Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med* 2013;14:744–8.
- [21] Postuma RB, Gagnon JF, Montplaisir JY. REM sleep behavior disorder: from dreams to neurodegeneration. *Neurobiol Dis* 2012;46:553–8.
- [22] Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain* 2007;130:2770–88.
- [23] Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol* 2013;12:443–53.
- [24] Pizzi F, Ferri R, Poli F, Vandi S, Cosentino FI, Plazzi G. Polysomnographic study of nocturnal sleep in idiopathic hypersomnia without long sleep time. *J Sleep Res* 2013;22:185–96.